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| 10/564,347 | 01/11/2006 | Annette S. Kim | 21159P | 9097 |

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

| EXAMINER | |
|---|---|
| SHIAO, REI TSANG | |

| ART UNIT | PAPER NUMBER |
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| 1626 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/564,347 | KIM ET AL. | |
| | Examiner | Art Unit | |
| | Rei-tsang Shiao, Ph.D. | 1626 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/03/08, 4/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**1.** This application claims benefit of the provisional application:

60/489,630 with a filing date 07/24/2003.

**2.** Amendment of claims 1-7, 13 and cancellation of claims 14-15 and 18-30 in the amendment filed on March 03, 2008 is acknowledged. Claims 1-13 and 16-17 are pending in the application.

### *Information Disclosure Statement*

**3.** Applicant's Information Disclosure Statements, filed on March 03, 2008 and April 25, 2006 have been considered. Please refer to Applicant's copies of the 1449's submitted herein.

### *Responses to Election/Restriction*

**4.** Applicant's election without traverse of election of Group I claims 1-13 and 16-17, in part, in the reply filed on March 03, 2008 is acknowledged. An election of a species, i.e., benzyl 4-ethyl-2-formyl-5-phenyl-1H-pyrrole-3-carboxylate, is also acknowledged. Claims1-13 and 16-17 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 1-13 and 16-17, in part, drawn to compounds/compositions of formula (I), wherein the variables R1-R3 independently do not represents heteroaryl or heterocycle thereof, the variables R1-R3 independently independently are not substituted with heteroaryl or heterocycle thereof, and their methods of use.

Claims 1-13 and 16-17, in part, embraced in above elected subject matter, are prosecuted in the case. Claims 1-13 and 16-17, in part, not embraced in above elected subject matter, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper.

***Claim Rejections - 35 USC § 112***

**5.** The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-13 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using compounds of formula (I) for treating cells *in vitro*, it does not reasonably provide enablement for using compounds of the formula (I) for treating PK-related disorders, retinal vascularization, or cancer *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case:

**The nature of the invention**

The nature of the invention of claims 9-13 and 16-17 is drawn to intent methods of use using compounds of formula (I) for treating PK-related disorders, retinal vascularization, or cancer *in vitro* or *in vivo*.

**The state of the prior art and the predictability or lack thereof in the art**

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each

embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Palmer et al. CAS: 126:277441, disclose a tyrosine Kinase Inhibitors and evaluation for its inhibition of the tyrosine kinase activity of the isolated epidermal growth factor receptor (EGFR) and of its autophosphorylation in EGF-stimulated A431 cells. Applicants are claiming intent methods of use using compounds of formula (I) effective to "treating PK-related disorders, retinal vascularization, or cancer" *in vivo*. As such, the specification fails to enable the skilled artisan to use the compounds of claims 9-13 and 16-17 effective to "treating PK-related disorders, retinal vascularization, or cancer" *in vivo*.

In addition, there is no established correlation between *in vitro* activity and accomplishing treatment of "treating PK-related disorders, retinal vascularization, or cancer", *in vivo*, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the ad would not be able to use the compounds of the formula (I) since there is no description of an actual method wherein "treating PK-related disorders, retinal vascularization, or cancer" *in vivo* in a host is treated.

Hence, one of skill in the art is unable to fully predict possible results from the administration of the compounds of claims 9-13 and 16-17 due to the unpredictability of the "treating PK-related disorders, retinal vascularization, or cancer" *in vivo*. The "treating PK-related disorders, retinal vascularization, or cancer" *in vivo* is known to

have many obstacles that would prevent one of ordinary skill in the art from accepting treating or preventing regimen on its face.

**The amount of direction or guidance present and the presence or absence of working examples**

The only direction or guidance present in the instant specification is the listing of exemplary kinase assays, *in vitro*, see pages 90-94 of the specification. There are no *in vivo* working examples present for the treatment of PK-related disorders, retinal vascularization, or cancer ameliorated by inhibiting kinase activity by the administration of compounds of the instant invention.

**The breadth of the claims**

The breadth of the claims is methods of use of the instant compounds effective to "treating PK-related disorders, retinal vascularization, or cancer" *in vitro or in vivo*.

**The quantity of experimentation needed**

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what "treating PK-related disorders, retinal vascularization, or cancer" *in vivo* would be benefited (i.e., treated) by the administration of the instant compounds of the instant invention and would furthermore then have to determine which of the claimed methods of use would provide treatment of PK-related disorders *in vivo* by inhibiting kinase activity, if any.

**The level of the skill in the art**

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which methods of use exhibit the desired pharmacological activity and which diseases would benefit from this activity. Thus, the specification fails to provide sufficient support of the broad use of the pharmaceutical compounds of the instant claims 9-13 and 16-17 for the "treating PK-related disorders, retinal vascularization, or cancer" *in vivo* by inhibiting kinase activity". As a result necessitating one of skill to perform an exhaustive search for which "treating PK-related disorders, retinal vascularization, or cancer" *in vivo* by inhibiting kinase activity", can be treated by what pharmaceutical compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success. This rejection can be

overcome by incorporation of the treated conditions (i.e., *in vitro*) into claims 9-13, and deletion of claims 16-17 would obviate the rejection.

***Claim Rejections - 35 USC § 103***

**6.** The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

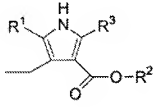
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 and 16-17 are rejected under 35 U.S.C. 103(a) as being obvious over Trotter et al. WO 2003035615.

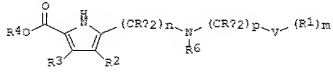
Applicants claim compounds/compositions of formula (I), i.e.,



, wherein the variables $R^1$- R3 independently represents substituted or unsubstituted alkyl, see claim 1.

***Determination of the scope and content of the prior art (MPEP §2141.01)***

Trotter et al. disclose compounds/compositions of formula (I), i.e.,



, wherein the variable R2-R4 independently represents alkyl, see pages 2-9.

***Determination of the difference between the prior art and the claims (MPEP §2141.02)***

The difference between the instant claims and Trotter et al. is that Trotter et al. compounds/compositions of formula (I) are isomers of the instant invention. The –C(O)OR2 moiety of the instant invention is at the 4' position of formula (I), while Trotter et al. '615 is at the 1' position.

***Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)***

One having ordinary skill in the art would find the instant claims 1-13 and 16-17 prima facie obvious **because** one would be motivated to employ compounds/ compositions of Trotter et al., wherein –C(O)OR2 moiety of formula (I) is at the 4' position. Nothing unobvious is seen in substituting the known claimed isomer for the structurally similar isomer (i.e., structure isomers), as taught by Kim et al., since such structurally related compounds suggest one another and would be expected to share common properties (i.e., chemotherapeutic agents or compositions) absent a showing of unexpected results, see *In re Norris*, 84 USPQ 458 (1950). Dependent claims 2-13 and 16-17 are also rejected along with claim 1 under 35 U.S.C. 103(a).

The motivation to obtain the claimed catalyst derives from known Trotter et al. compounds/compositions would possess similar activity (i.e., pharmaceutical compositions) to that which is claimed in the reference.

***Double Patenting***

**7**. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with37 CFR 3.73(b).

Claims 1-13 and 16-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of Kim et al. co-pending application No. 10/564,030. Although the conflicting claims are not identical, they are not patentably distinct from each other and reasons are as follows.

Applicants claim compounds/compositions of formula (I), see claim 1.

Kim et al. '030 claim compounds/compositions of formula (I).

The difference between the instant claims and Kim et al. is that Kim et al. compounds/compositions of formula (I) are isomers of the instant invention. The

–C(O)OR2 moiety of the instant invention is at the 4' position of formula (I), while Kim et al. '030 is at the 1' position.

One having ordinary skill in the art would find the instant claims 1-13 and 16-17 prima facie obvious **because** one would be motivated to employ compounds/ compositions of Kim et al., wherein –C(O)OR2 moiety of formula (I) is at the 4' position. Nothing unobvious is seen in substituting the known claimed isomer for the structurally similar isomer (i.e., structure isomers), as taught by Kim et al., since such structurally related compounds suggest one another and would be expected to share common properties (i.e., chemotherapeutic agents or compositions) absent a showing of unexpected results, see *In re Norris*, 84 USPQ 458 (1950). Dependent claims 2-13 and 16-17 are also rejected along with claim 1 under the obviousness-type double patenting.

The motivation to obtain the claimed catalyst derives from known Kim et al. compounds/compositions would possess similar activity (i.e., pharmaceutical compositions) to that which is claimed in the reference.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claims Objection***

**8.** Claims 1-13 and 16-17 are objected to as containing non-elected subject matter, i.e., heterocyclic or heteroaryl , isoxazole, benzofurane, furyl, pyridyl, thienyl, thiazole of

claim 5 -7, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on the pages 2-3 *supra*.

***Conclusion***

Any inquiry concerning this communication or earlier communications from theexaminer should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /

Rei-tsang Shiao, Ph.D.
Primary Patent Examiner
Art Unit 1626

April 29, 2008